each figure, fluorescent PCR products were generated by amplification of DNA obtained from normal (N) and tumor (T) tissue samples from the corresponding patient, and products were separated by size. For each tracing, the horizontal axis represents DNA fragment size, and the vertical axis (i.e. peak height) represents relative amount of each fragment. Figures 1Ai and 1Aii correspond to D8S264; Figures 1Aiii and 1Aiv correspond to LPL; Figures 1Av and 1Avi correspond to D8S136; and Figures 1Avii and 1Aviii correspond to FGFR1. Several fragment sizes (in base pairs) are indicated. --

Please delete the paragraph beginning at page 13, line 26, and ending at page 14, line 5, and substitute the following paragraph:

-- Figure 1B is a diagram which depicts a summary of LOH analyses described herein. Results for each patient who exhibited LOH at least at one locus are shown. Filled circles represent loss of an allele. Circles containing a cross represent non-informative results owing to homozygosity at the corresponding locus. Open circles represent retention of both alleles. Cross-hatched areas of the diagram represent regions of allele loss. Hatched areas represent regions of non-informative results within the allele-loss area. The numbers atop each column refer to individual patients. The designations beside each row refer to polymorphic markers. The region near the marker *D8S261* locus, described herein, is boxed. --

At page 14, please delete the paragraph beginning at line 17 and ending at line 29, and substitute the following paragraph:

-- Figure 2 comprises Figures 2A, 2B, 2C, and 2D. The predicted Fez1 amino acid sequence (SEQ ID NO: 4) is depicted in Figure 2A. Figure 2A lists the predicted amino acid sequence of FEZ1 protein, as derived from the *FEZ1* cDNA. Underlined amino acid residues represent a region homologous to the DNA-binding domain of ATF-5 protein. Double-underlined amino acid residues represent a leucine zipper motif, in which repeated leucine residues are indicated. Heavily-underlined amino acid residues are residues which can be phosphorylated by either a cAMP/cGMP-dependent kinase (serine residue 29) or a tyrosine kinase-dependent kinase (tyrosine residue 67). Dashed-underlined regions represent regions

уЗ

B) out

having related amino acid sequence motifs. Serine and threonine residues in bold or thin dotted lines represent potential casein kinase II and protein kinase C, respectively, phosphorylation sites. -- Triangles indicate exon boundaries. Asterisks represent missense or nonsense mutation sites. --

At page 15, please delete the paragraph beginning at line 1 and ending at line 7, and substitute the following paragraph:

-- In Figure 2B, the predicted amino acid sequence of a region (amino acid residues 301-369; SEQ ID NO: 6) of Fez1 corresponding to the predicted DNA binding and leucine zipper regions is compared with the analogous regions (SEQ ID NOs: 7 and 8, respectively) of proteins Atf-5 and KIAA0522. Identical amino acid residues are indicated by double underlining, and similar amino acid residues are indicated by single underlining. Gaps introduced by the FASTA program are represented by "-". Closed circles are used to indicate repeated leucine residues. --

At page 17, please delete the paragraph beginning at line 6 and ending at line 16, and substitute the following paragraph:

-- Figure 4 comprises Figures 4A and 4B. Figure 4A is a diagram which depicts truncated *FEZ1* transcripts observed in cancer cells, as described herein. The normal exon/intron structure is indicated on the top line of the diagram, and was determined by sequencing of normal (i.e. non-cancerous) brain, prostate and esophagus cDNAs and by sequencing *FEZ1* gene in BAC. Boxes represent exons; the hatched areas represent the open reading frame (1788 base pairs; SEQ ID NO: 3). Horizontal lines represent introns, and closed circles represent point mutations which were observed, as described herein. The boxed notation "LZ" represents the approximate location of the leucine-zipper motif described herein. "FS" represents the approximate position of a frame-shift described herein. Aberrant transcripts observed in tumors are depicted by bold lines on the lines below the top line in the diagram. --

35

At page 17, please delete the paragraph beginning at line 17 and ending at line 20, and substitute the following paragraph:

-- Figure 4B is the putative amino acid sequence (SEQ ID NO. 5) encoded by the frame-shifted *FEZ1* transcript having a molecular weight of about 8.6 kilodaltons. Amino acid residues encoded by the frame-shifted portion of the transcript are underlined. --

Please delete the paragraph beginning at page 17, line 21, and ending at page 18, line 24, and substitute the following paragraph:

-- Figure 5, comprising Figures 5A-1 to 5Q, is a series of nucleotide and amino acid sequences. Figure 5A comprises Figures 5A-1 to 5A-6, and lists the nucleotide sequence (SEQ ID NO: 1) of a portion of the human genome comprising the FEZ1 gene. Figure 5B comprises Figures 5B-1 to 5B-4, and lists the nucleotide sequence (SEQ ID NO: 2) of a cDNA which reflects the nucleotide sequence of the full-length mRNA transcript of wild type FEZ1. Figure 5C lists the nucleotide sequence (SEQ ID NO: 9) of a cDNA which reflects the nucleotide sequence of the ORF region of a truncated (E16T8) FEZ1 mRNA transcribed by tumors cells. Figure 5D lists the nucleotide sequence (SEQ ID NO: 10) of a cDNA which reflects the nucleotide sequence of the ORF region of a truncated (E264162) FEZ1 mRNA transcribed by tumors cells. Figure 5E comprises Figures 5E-1 and 5E-2, and lists the nucleotide sequence (SEQ ID NO: 11) of a cDNA which reflects the nucleotide sequence of the ORF region of a truncated (T8D145M4) FEZ1 mRNA transcribed by tumors cells. Figure 5F comprises Figures 5F-1 and 5F-2 and lists the nucleotide sequence (SEQ ID NO: 12) of a cDNA which reflects the nucleotide sequence of the ORF region of a truncated (D14) FEZ1 mRNA transcribed by tumors cells. Figure 5G comprises Figure 5G-1 and 5G-2 and lists the nucleotide sequence (SEO ID NO: 13) of a cDNA which reflects the nucleotide sequence of the ORF region of a truncated (G3611) FEZ1 mRNA transcribed by tumors cells. Figure 5H comprises Figures 5H-1 and 5H-2, and lists the nucleotide sequence (SEQ ID NO: 14) of a cDNA which reflects the nucleotide sequence of the ORF region of a truncated (G3612) FEZI mRNA transcribed by tumors cells. Figure 5I comprises Figures 5I-1 and 5I-2 and lists the nucleotide sequence (SEQ ID NO: 3) of a cDNA which reflects the nucleotide sequence of the ORF region of wild type FEZ1 mRNA.

Figure 5J comprises Figures 5J-1 to 5J-5 and lists the amino acid sequence (SEQ ID NO: 4) of full-length, human wild type Fez1 protein. Figure 5K lists the amino acid sequence (SEQ ID NO: 15) of a truncated (E16T8) Fez1 protein expressed by tumors cells. Figure 5L comprises Figures 5L-1 and 5L-2 and lists the amino acid sequence (SEQ ID NO: 16) of a truncated (E264162) Fez1 protein expressed by tumors cells. Figure 5M comprises Figures 5M-1 to 5M-4 and lists the amino acid sequence (SEQ ID NO: 17) of a truncated (T8D145M4) Fez1 protein expressed by tumors cells. Figure 5N comprises Figures 5N-1 to 5N-4 and lists the amino acid sequence (SEQ ID NO: 18) of a truncated (D14) Fez1 protein expressed by tumors cells. Figure 5O comprises Figures 5O-1 to 5O-5 and lists the amino acid sequence (SEQ ID NO: 19) of a truncated (G3611) Fez1 protein expressed by tumors cells. Figure 5P comprises Figures 5P-1 to 5P-5 and lists the amino acid sequence (SEQ ID NO: 20) of a truncated (G3612) Fez1 protein expressed by tumors cells. Figure 5Q lists the nucleotide sequence (SEQ ID NO: 21) of the F37 probe described herein. --

At page 19, please delete the paragraph beginning at line 1 and ending at line 4, and substitute the following paragraph:



-- Figure 7, comprising Figures 7A (clone 15), 7B (clone 54), 7C (clone 18), and 7D (clone 118), is a quartet of graphs which indicate the time dependence of the ratio of transfected MCF7 clone cell number to control cell number for cells maintained in tetracycline-free medium containing 10% (⋄), 5% (⋄), 2.5% (□), 1% (■), or 0.5% (▲) (v/v) fetal bovine serum. --

At page 20, please delete the paragraph beginning at line 1 and ending at line 4, and substitute the following paragraph:



-- Figure 14, comprising Figures 14A, 14B, 14C, and 14D, is a series of four images which depict the results of immunoblotting experiments involving HeLaS3 cells which were co-transfected with a vector encoding a V5/Fez1 fusion protein and a vector encoding an EXP/EF1-γ fusion protein. --

At page 26, please delete the paragraph beginning at line 16 and ending at line 21, and substitute the following paragraph:

-- By describing two polynucleotides as "operably linked", it is meant that a single-stranded or double-stranded nucleic acid moiety comprises the two polynucleotides arranged within the nucleic acid moiety in such a manner that at least one of the two polynucleotides is able to exert a physiological effect by which it is characterized upon the other. By way of example, a promoter operably linked with the coding region of a gene is able to promote transcription of the coding region. --

At page 29, please delete the paragraph beginning at line 10 and ending at line 16, and substitute the following paragraph:

-- A "gene chip" is a manufacture comprising a surface having an ordered array of polynucleotides attached thereto, either permanently or reversibly. For example, the ordered array may comprise four sections, wherein one of four polynucleotides is attached to the surface in each section, and wherein the four polynucleotides have nucleotides sequences which are identical with the exception of one nucleotide residue (e.g. 5'-AACCAAAAAAA-3' (SEQ ID NO. 61); 5'-AACCAAAAAAA-3' (SEQ ID NO. 62); 5'-AACCAAAAAAA-3' (SEQ ID NO. 63); and 5'-AACCAAAAAAAA-3' (SEQ ID NO. 64). --

At page 56, please delete the paragraph beginning at line 10 and ending at line 24, and substitute the following paragraph:

--The invention includes a method of determining the cancerous status of a sample tissue. This method comprises comparing *FEZ1* expression in the sample tissue with *FEZ1* expression in a control tissue of the same type. Decreased *FEZ1* expression in the sample tissue, relative to *FEZ1* expression in the control tissue, is an indication that the sample tissue is cancerous. The sample tissue can be a phenotypically abnormal tissue (e.g. a biopsy sample obtained from a potentially cancerous lesion in a human tissue such as breast or prostate), or it can be a phenotypically normal tissue. The control tissue is a non-cancerous tissue of the same type, and can be obtained from the same human from whom the sample tissue was obtained, or

2014

from one or more humans different than the one from whom the sample tissue was obtained. If a body of data exists or is created, from which a representative value for expression of FEZ1 in non-cancerous tissue of the same type as the sample tissue, then FEZ1 expression in the sample tissue can be compared with this representative value, rather than performing a separate determination of FEZ1 expression in the same or a different human. --

At page 106, please delete the paragraph beginning at line 10 and ending at line 24, and substitute the following paragraph:

-- The effect of *FEZ1* expression *in vitro* cell growth of MCF7 cells was analyzed using the CellTiter 96[™] Aqueous non-radioactive cell proliferation assay obtained from Promega Corporation (Madison, WI) per the supplier's instructions. The absorbance of the MTS compound of the assay system at 490 nanometers exhibited a linear correlation between the number of MCF7 cells in a range between 102 and 104 cells, as confirmed by cell counting in which dead cells were excluded by tryptan blue staining. Cells of clones 15, 18, 54, and 118 were selected in wells of 96-well plates containing tetracycline-free medium supplemented with 10, 5, 2.5, 1, or 0.5% (v/v) FBS. Culture medium was exchanged daily with the corresponding fresh medium. Absorption at 490 nanometers was assessed in order to estimate the number of cells present in each well at selected times. The results of these experiments are presented in Figure 7, in which data are shown as a ration of the number of transfected cells to the number of control mock MCF7 transfectants (i.e. transfected with vector alone) cultured in the corresponding medium. Data were calculated as an average of four independent experiments, and bars in Figure 7 indicate the standard deviations. --

At page 107, please delete the paragraph beginning at line 11 and ending at line 19, and substitute the following paragraph:

-- About 5×10^6 or about 2×10^7 cells (MCF7 cells transfected with the pTet-OffTM vector alone o rMCF7 transfectant clone 15, 18, 56, or 118 clone cells) were subcutaneously inoculated into the left dorsal subclavicular region of 6 week-old female Balb/nude mice. Four mice were used for each experimental group. Tumor volume was

BIL